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CLINICAL TRIAL REPORT

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A combination of ifosfamide and mitoxantrone as salvage therapy in patients with advanced ovarian cancer

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Abstract Ifosfamide (IFX) and mitoxantrone (MXN) have been found to be effective against advanced epithelial ovarian cancer. The combination of these two agents has not yet been tested in this setting but seems to be rational, given the different action mechanisms of these drugs and their not completely overlapping side effects. Between June 1987 and November 1991, 37 patients with advanced ovarian carcinoma recurrent or refractory to primary cisplatin-based chemotherapy entered the study. Therapy consisted of MXN, given i.v. at 10 mg/m^2 on day 1 and IFX given i.v. at 2,000 mg/m^2 per day on days 1–3 with mesna. The cycles were repeated every 3 weeks. Four patients achieved a complete remission and three achieved a partial remission, for response rates of 18.9% [95% confidence interval (CI) 6.3–31.5%] in the whole sample and 38.8% (95% Cl 16.3–61.3%) in the subset of 18 patients responding to first-line cisplatin. No response was obtained in the remaining patients, whose disease was refractory to primary platinum-based chemotherapy. Clinically significant toxicity (WHO grades 3–4) included leukopenia in 46% of the patients and anemia in 32.5%. The non-hematologic toxicity was mild, except for reversible alopecia (57%) and nausea and vomiting (48.5%). This regimen seems attractive for patients who have either failed or not received platinum retreatment, especially when limiting neurotoxicity occurs. Further studies are warranted to establish the relative impact of both of these agents.

Key words Epithelial ovarian cancer · Ifosfamide · Mitoxantrone

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Introduction

Ovarian cancer is a relatively chemosensitive tumor. Although the rate of response to first-line cisplatin-based regimens is around 60–80% [13], only 25% of the patients with advanced disease survive for 5 years [17]. Thus, the majority of these patients suffer disease recurrence following the response to initial chemotherapy. The rate of response to second-line single agents and combinations has been disappointing in patients who have failed to achieve a complete remission with first-line platinum-based chemotherapy [15]. In addition, most of the responses are partial and of relatively short duration.

For ovarian cancer patients who have experienced disease recurrence or whose disease is refractory to primary cisplatin-based chemotherapy, more active agents and combinations with few overlapping toxic effects are needed. Considerable effort is therefore being made to identify new chemotherapeutic drugs with novel chemical structures that are not cross-resistant with the commonly employed agents.

Ifosfamide (IFX) is an analog of cyclophosphamide that has shown evidence of activity in ovarian cancer and a lack of cross-resistance with cyclophosphamide in various tumor sites [1]. Since the introduction of mesna, IFX has been shown to be highly active in a variety of solid tumors [1]. In a phase II trial carried out in patients with ovarian carcinoma refractory to cisplatin-containing therapy or progressive after an initial response to such treatment, the Gynecologic Oncology Group (GOG) reported an overall response rate (OR) of 20% [complete response (CR) rate 7%, partial response rate (PR) 13% [16].

Mitoxantrone (MXN), a synthetic aminoanthraquinone whose activity appears to be mediated by intercalation into the DNA double helix, has shown significant activity in vitro against human ovarian cancer [14]. The results of clinical studies on ovarian cancer have been contradictory. Disappointing results

were observed in two different studies carried out by the Southwest Oncology Group (no response in 31 evaluable patients) [6] and by the GOG (1 response in 26 patients) [12]. Lawton et al. [7], instead, reported a 24% response rate in a series of 41 patients who had failed previous chemotherapy.

The combination of IFX and MXN has been tested in different solid tumors, including lymphomas [9], lung cancer [3], and soft-tissue sarcomas [8]. On the basis of these clinical data and given the lack of cross-resistance and overlapping toxicity, we initiated this phase II study in patients with relapsing or refractory ovarian cancer to evaluate the combination of MXN and IFX together with mesna uroprotection as salvage chemotherapy and to determine its toxicity, response rate, and response duration.

Patients and methods

Patients with histologically confirmed epithelial ovarian carcinoma relapsing or refractory to cisplatin-containing combination therapy were eligible for this study. Additional eligibility criteria included the presence of disease measurable by physical examination, computed tomography (CT) scan, and ultrasonography or X-ray. Ascites and pleural effusions were not considered measurable disease. An Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; an interval of at least 4 weeks since prior chemotherapy and adequate hematologic (WBC $\geq$ 4,000 cells/ml, platelet count $\geq$ 100,000 cells/ml), hepatic (serum bilirubin $\leq$ 1.5 mg/dl, SGOT and alkaline phosphatase $\leq 2 \times$ normal), and renal (serum creatinine $\leq$ 1.5 mg/dl or creatinine clearance $\geq$ 60 ml/min) function tests were also required. Oral informed consent was obtained from all patients.

Criteria for exclusion were prior therapy with IFX or MXN; a prior cumulative dose of Adriamycin exceeding 300 mg/m^2; the presence of a second malignancy, excluding squamous or basal skin lesions; active infections; central nervous system involvement; an age of >70 years; and the presence of significant heart disease.

A history and a physical examination with assessment of evaluable lesions, ECOG performance status (PS), EKG, complete blood count (CBC), blood chemistry and urinalysis were performed before each cycle of therapy. A weekly CBC was obtained thereafter. Tumor assessment by imaging studies (mainly CT scanning) was carried out at every other course. Standard response criteria were employed [11].

MXN was given at a dose of 10 mg/m^{2}on day 1 by i.v. infusion over 30 min in 100 ml 5% dextrose. IFX was given i.v. in 500 ml Ringer's solution over 30 min at a daily dose of 2,000 mg/m^2 on days 1–3. Adequate hydration (2,000 ml 5% dextrose given as a 4-h infusion after IFX administration) together with mesna uroprotection (500 mg/m^2 given by i.v. bolus before and 4 h after the daily IFX infusion) and antiemetic drugs were provided. The regimen was repeated every 3 weeks.

A 20% dose reduction for both drugs was made for WHO grade 4 myelotoxicity or for any prolonged myelosuppression. Treatment was restarted only after full hematologic recovery.

Patients were considered evaluable for response if they had received at least two courses; however, those showing early progression were considered treatment failures. All patients were evaluable for toxicity. Patients remained in the study until disease progression was noted or adverse effects prevented further therapy.

Results

Between June 1987 and November 1991, 37 patients who met all the eligibility requirements entered the study, and all were assessable for response and toxicity. The median age was 55 (range 39–70) years and the median PS was 1 (range 0–2). The histology included: serous (14), mucinous (4), endometrioid (3), not otherwise specified (15) adenocarcinoma, and clear-cell tumor (1).

Most patients (22) had been heavily pretreated. In all, 2 patients received 3 regimens, 19 received 2, and the remaining 16 received only first-line treatment. Primary chemotherapy included cisplatin given in all cases in combination with cyclophosphamide (29 patients) either alone or with other agents (doxorubicin in 11 patients, methotrexate in 3, and etoposide in 3). In all, 24 patients had never been treated with anthracyclines and 5 had never received alkylating agents. In addition, 4 patients received prior radiotherapy.

The median interval between primary chemotherapy and first retreatment was 6 (range 1–101) months for the whole sample of patients and 19.5 (range 5–101) months for the platinum-responder subgroup. At study entry, all patients presented bulky disease. Overall, 17 had pelvic disease and 20 had both pelvic and extrapelvic disease (15 with liver metastases, 3 with neoplastic pleural effusion, and 2 with lung metastases). No patient had extrapelvic disease alone. A median of two courses (range 1–6) were given.

In all, 4 patients achieved a CR and 3 achieved a PR, for an OR rate of 18.9% [95% confidence interval (CI) 6.3–31.5%]. In addition, 5 patients (13.5%) had stable disease (SD). Altogether, 9 patients received only 1 course of treatment because of rapidly progressive disease. The median duration of the CRs and PRs was 15.5 and 5 months, respectively. The median duration of survival was 7 (range 2–69+) months for all 37 patients and 19 (range 6–69+) months for the responding patients. One complete responder is alive at 69 months from the start of therapy and remains relapse-free. Only one of the nonresponders is alive at 41 months. All the responders had a PS of 0–1 and all achieved a clinical or pathological remission with first-line cisplatin treatment (also including cyclophosphamide in seven cases and doxorubicin in three).

Three of the seven responses were observed in patients with pelvic disease, three were seen in patients with pelvic disease and liver metastases, and one was observed in a patient with pelvic disease and lung metastases. A median of 6 (range 3–6) courses was given to the responders. Three responder patients had received two prior chemotherapy regimens and four patients only one prior regimen.

Table 1 Response to the IFX-MXN combination according to prior chemotherapy outcome (*DDP* Cisplatin)

1st-line DDP chemotherapy	2nd-line chemotherapy Response		Response to IFX-MXN
Responders	Platinum derivatives	6/8	2/8[a]
$n = 18$	Alkylating agents	0/3	1/3
	No treatment	7	4/7
Nonresponders	Platinum derivatives	0/6	0/6
$n = 19$	Others	0/2	0/2
	No treatment	11	0/11

[a] Both patients failed 2nd-line chemotherapy

Table 2 Toxicity of IFX plus MXN

	Number of patients (%) WHO grade			
Toxicity	1	2	3	4
Leukopenia	4 (11)	5 (13.5)	12 (32.5)	5 (13.5)
Thrombocytopenia	1 (3)	1 (3)	–	–
Anemia	15 (40.5)	7 (19)	1 (3)	11 (29.5)
Nausea & vomiting	2 (5.5)	9 (24.5)	14 (38)	4 (10.5)
Stomatitis	–	3 (8)	1 (3)	–
Alopecia	4 (10.5)	5 (13.5)	21 (57)	–

According to the prognostic subsets defined by Hansen et al. [5], the results obtained in the present study may be summarized as follows (Table 1):

1. No response to the IFX-MXN salvage chemotherapy was observed in the 19 patients failing first-line cisplatin chemotherapy.
2. Of the 11 first-line platinum-responder patients receiving second-line chemotherapy before starting salvage IFX-MXN, 6 achieved a second response (6 of 8 treated with platinum derivatives and none of the 3 treated with other agents). However, none of the 6 responders achieved a further response to the third-line IFX-MXN combination (which, instead, included 2 of 8 responders in the former subgroup and 1 of 3 in the latter).
3. Of the remaining 7 platinum-responder patients receiving salvage IFX-MXN as second-line chemotherapy, 4 responded.

Clinically significant toxicity (WHO grades 3–4) included the following (Table 2) : leukopenia in 17 patients (46%) and anemia in 12 patients (32.5%). The non-hematologic toxicity was mild, except for reversible alopecia (57%) and nausea and vomiting (48.5%). One patient experienced lethargy and confusion on the 3rd day of the first course, although neurotoxicity reversed within 24 h of the discontinuation of IFX. Reversible grade 3 nephrotoxicity was found in one patient and diarrhea (grade 3) was observed in another. Myelotoxicity required treatment delays in 13 patients (35%) and dose reductions in 5 (13.5%).

Discussion

The inadequacy of salvage chemotherapy in epithelial ovarian cancer has long been recognized. In 1977, Stanhope et al. [15] reviewed drug therapy in patients failing first-line treatment with alkylating agents and reported virtually no response. Similar results have been obtained with phase II agents since cisplatin was incorporated into primary regimens in the late 1970s. The GOG identified no agent showing antitumor activity exceeding an OR of 20% in patients with ovarian cancer.

It has been suggested that the likelihood of response to salvage chemotherapy is strongly related to the outcome of prior first-line cisplatin chemotherapy, with increasing frequency of responses occurring in patients with longer treatment-free interval. In a retrospective study, Markman et al. [10] observed a 43% OR rate in 72 evaluable patients receiving salvage chemotherapy with platinum derivatives after relapse (not earlier than 4 months) following a prior response to cisplatin-based chemotherapy. Patient selection is therefore the most critical issue in the evaluation of salvage chemotherapy in ovarian cancer.

According to Hansen et al. [5], current salvage chemotherapy (with either platinum retreatment or other agents and combinations) is ineffective in patients failing primary cisplatin chemotherapy, even though promising results have been reported for both Taxol [18] and Taxotere [4] (30% response rate, duration of response 4–5 months). When only patients with true resistance to first-line platinum-based chemotherapy (and, by definition, those who never respond to additional platinum treatment) are included, this rate is significantly lower (17% for Taxol) [2].

For the platinum-responder patients, instead, the first choice for platinum retreatment should be emphasized (in the present study, 6 of 8 responded). In view of the high response rate (7/18, 38.8%) observed in the subset of patients whose disease was initially nonrefractory to cisplatin, the IFX-MXN combination seems attractive for patients who either have failed or are not eligible for platinum retreatment because of persistent subacute toxicity (such as peripheral neurotoxicity).

The results of the present study carried out in heavily pretreated patients demonstrate that the IFX-MXN combination has an antitumor activity (OR 19%) similar to that of either of these agents employed alone.

Myelosuppression (especially leukopenia) was the dose-limiting toxic effect, causing treatment delay and dose attenuation. Further studies are warranted to establish both the antitumor activity and the toxic effects of these two agents. The importance of patient selection for salvage chemotherapy trials should be greatly emphasized.

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